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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,796	HIRSCH ET AL.	
	Examiner	Art Unit	
	Brandon J Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5 and 8-21* is/are pending in the application.

4a) Of the above claim(s) *5,8-12 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-15 and 17-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The Election filed on June 21, 2004 in response to the Office Action of May 5, 2004 is acknowledged and has been entered. Claims 1-4 and 6-7 have been cancelled. Claims 5, 8-12 and 13-21 are pending in the application and Claims 5 and 8-12 have been withdrawn from further consideration by examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Newly submitted claim 16 is directed to an invention that is independent or distinct from the invention originally claimed for the following reason: claim 16 includes a limitation drawn to non-elected subject matter: administration of erythropoietin etc. Accordingly, claim 16 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Claims 13-15 and 17-21 and the elected species anthracyclines are currently under consideration.

Applicant's election with traverse of Group I, claims 1-4 and 6-7, the use of compounds which inhibit the activation of NF-kB, wherein said compound is SEQ ID NO: 2 has been acknowledged. The traversal is on the ground(s) that the subject matter that is recited in the claims of the present national stage application was subject to examination during the international stage application. The international Examiner found no lack of unity, applying the same legal standard to similar facts. As a result, applicants believe that the U.S. Patent Office cannot now contend that examination of the pending claims in the present application imposes an undue burden, especially since the U.S. Examiner has had the considerable benefit of the search results generated by the international Examiner, on the basis of the subject matter. These arguments have been considered but are not found persuasive as such arguments do not apply when restriction is required under 35 USC 121 and 372, as in the instantly filed application. Thus, when the Office considers international applications as an International Searching Authority, as an International Preliminary Examining Authority, and during the national stage as a Designated or Elected Office under 35 U.S.C. 371, only PCT Rule 13.1 and 13.2 will be followed when considering unity of

invention of claims of different categories without regard to the practice in national applications filed under 35 U.S.C. 111. Thus, it is maintained that the technical feature linking the inventions of Groups I-IV does not constitute a special technical feature as defined by PCT Rule 13.2 and does not define a contribution over the prior art for the reasons of record.

For these reasons, the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 1-4 and 6-7 have been cancelled.

Claims 5, 8-21 are currently pending in the application.

Claims 5, 8-12, and 16 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 13-15 and 17-21 and the elected species anthracyclines are currently under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-15 and 17-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14 and 20-21 recites the limitation "said compounds" in claim 13. There is insufficient antecedent basis for this limitation in the claim.

Claim 17-19 recites the limitation "said growth hormone" in claim 13. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 is indefinite because it recites the phrase "adapted to activate". Adapted to activate is not defined by the claim (which reads on one or several cytotoxic molecules adapted to activate NF-kB). Although the specification provides several cytotoxic molecules adapted to activate NF-kB (page 8, lines 10+), it does not provide a limited definition for ascertaining the requisite degree of adaptation sought in the claims and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention and would not be able to determine the metes and bounds of the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-15, 17, and 20-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of a genus of NF-κB inhibitors, and a genus of compounds that activate NF-κB referred to as "cytotoxic" molecules.

The specification teaches (page 5, lines 15+) that by compounds inhibiting the activation of NF- κB (also called NF-B inhibitor compounds), there is meant any compound capable of inhibiting in the cells of the organism, the activation of NF- κB caused by a cytotoxic molecule. The specification (page 6, lines 4+) further teaches that NF- κB inhibitors are any compounds which bind specifically to the transmembrane receptors of the cytokines of class I in the cells or the organism selected from growth hormone, prolactin, erythropoietin, interleukin-4.... With regards to the "NF- κB" inhibitor being growth hormone, the specification teaches that growth hormone includes not only human growth hormone (SEQ ID No: 2) but any peptide sequence derived by addition and/or deletion and/or substitution of one or several amino acids of the sequence of SEQ ID NO: 2. With regards to cytotoxic molecules, the specification teaches (page 8, lines 10+) that cytotoxic molecules adapted to activate the NF- κB factor used in association with compounds inhibiting the activation of NF- κB can be cited: cytokines; the anthracyclines, of which may be mentioned daunomycin, and dauxorubicun; vinca-alkaloids, such as vinblastine and vincristin,; and paclitaxel (or Taxol, DCI) . However, the written description (page 16, Example 4) only reasonably conveys one species of growth hormone (human growth hormone (hGH), SEQ ID NO:2) in combination with anthracyclines for methods of treating non-lymphoid tumor cells and therefore, does not commensurate the full scope of any and all compounds or nucleotide sequences derived by degeneracy of the genetic code of SEQ ID NO: 1 or any peptide sequence derived by addition and/or deletion and/or substitution of one or several amino acids of the sequence of SEQ ID NO: 2.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of NF-B inhibitors that encompass the genus of compounds that inhibit NF- κB activation nor does it provide a description of structural features that are common to the inhibitors. Further, the specification fails to provide a representative number of cytotoxic molecules that encompass the genus of compounds along with a description of structural features that are common to the cytotoxic molecules. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of one species of inhibitor and activator is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus of NF- κB inhibitors and cytotoxic molecules, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a NF- κB inhibitor wherein said NF-kB inhibitor is human growth hormone (SEQ ID NO:2) and a cytotoxic molecule wherein said cytotoxic molecule is an anthracycline, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 13, 15, 17, and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Wong et al. (US Patent No 5725851, March 1995).

Claims 13, 15, 17 and 20 are drawn to a method of treating a patient with a pathology selected from the group consisting of malignant hemopathies and solid tumors comprising administering an effective amount of a compound that inhibits NF- κB, wherein said compound inhibiting NK- κB activation is human growth hormone (claim 17). The method further comprises administering one or several cytotoxic molecules which activate NF-κB, wherein said cytotoxic molecule is an anthracyclines.

Wong teaches hGH used together with radiation and/or chemotherapy in the treatment of luekemias as well as other cancers known to be susceptible to radiation and chemotherapy treatment (7^{th} column, lines 50+). Wong further teaches that hGH is administered prior and/or after exposure to a cytotoxin and that the efficacy of the agent will vary depending on the dose and time course of the chemotherapy (column 8, line 19+). With regards to hGH, the patent defines the term "hGH" as human growth hormone which

covers biologically active human growth hormone equivalents, e.g. those differing by one or more amino acids in the overall sequence (5th column, lines 8+). With regards to chemotherapy, Wong defines (6th column, lines 46+) chemotherapy as the administration of an agent to exert toxic effect on rapidly proliferating cell in comparison to differentiated, mature and slower growing cells, wherein said agent includes the patently disclosed anthracyclines. Further, Wong teaches that growth hormone exerts its action through interaction with specific receptors on cell membranes (1st column, lines 59-61). Therefore, the claimed functional limitation of treating a patient with a pathology by inhibiting NF- κB activation or activating NF-κB by a cytotoxic agent would be an inherent property of using hGH and a cytotoxic molecule for cancer treatment. In addition, although the reference does not specifically teach human growth hormone (hGH) being obtained by extraction from hypophysary extracts, the reference clearly teaches that "human growth hormone" covers all biologically active human growth hormone equivalents. Thus, it does not appear that the claims language or limitations results in a manipulative difference in the method steps when compared to the prior art disclosure. The patent office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claims 13-15, 17 and 20-21 are rejected under 35 U.S.C. 102(e) as being anticipated by Baldwin et al. (Pub. No. US 2002/0068690, October 1997).

Claims 13-15, 17, and 20-21 are drawn to a method for treating a patient with a pathology selected from the group consisting of malignant hemopathies and solid tumors comprising administering an effective amount of a compound that inhibits NF- κB (Claim 13). The method further comprises administering compounds to a patient who has become resistant to cytotoxic molecules (claim 14). The method further comprises administering one or several cytotoxic molecules to treat a pathology, wherein said cytotoxic molecule

which activates NF- κB factor (claim 15) is an anthracycline (claim 20). The method is than further characterized in that the dosage of the cytotoxic molecules administered in combination with said compounds that inhibit NF- κB is about 2 to about 5 times less than the dosage of said cytotoxic molecules administered alone in the scope of treatment of said pathology (claim 21).

Baldwin teaches a method of enhancing chemotherapeutic cytotoxicity in a subject treated with an antineoplastic chemotherapeutic agent, comprising administering to a subject a therapeutically effective amount of NF- κB inhibitor in conjunction with the administration of a chemotherapeutic agent (claim 6). Baldwin further defines a chemotherapeutic agents as the patentably disclosed anthracyclines, daunorubicin i.e. daunomycin (claim 8). The reference further teaches any type of cancer, tumor, or neoplasia may be treated by the methods of the present invention (page 6, 1st column, Paragraph 0054). Further, Baldwin teaches a therapeutically effective amount of an NF- κB such that the treated cell, or treated population of cells, is more susceptible to the apoptotic effects of a cytotoxic chemotherapy. This increased susceptibility of cells may be evidenced by the ability to decrease the dosage of the co-administered chemotherapeutic agent, compared to the dosage required in control cells treated without co-administered NF- κB (page 6, 2nd column, paragraph 0056). Although the reference does not specifically teach the dosage of the cytotoxic molecules administered in combination with the NF- κB inhibitor is about 2 to about 5 times less than the dosage of said cytotoxic molecule administered alone in the scope of treatment, the reference clearly teaches a reduction in the dose of the chemotherapeutic agent when co-administrated with the NF- κB inhibitor compared to one administered alone. In addition, the claimed functional limitation of a tumor cell being resistant to cytotoxic molecules would be an inherent property of the tumor cell. Thus, it does not appear that the claims language or limitations results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the

burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Hence, even though the claims are drawn to a mechanism by which pathology is treated by co-administration of a NF- κB inhibitor and a cytotoxic molecule, the claimed method does not appear to distinguish over the prior art teaching of the same or nearly the same method. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobviousness an otherwise known invention. In re Wiseman 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2nd 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Therefore, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
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BF

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PRIMARY EXAMINER